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FDA Questions for the Circulatory System Devices Panel
January 13, 2005
P040043
W.L. Gore & Associates, Inc.
GORE TAG Thoracic Endoprosthesis

Safety

Pivotal Study (TAG 99-01): The primary safety endpoint for the pivotal study was the proportion of subjects who experienced =1 major adverse event (MAE) through 1 year post-treatment. Comparisons were made between subjects treated with the original design of the GORE TAG Thoracic Endoprosthesis and open surgical repair.

The safety null hypothesis was that the proportion of subjects who experienced =1 major adverse event (MAE) through 1 year post-treatment was equal in the Control subjects and the TAG subjects. The alternate hypothesis was that the proportion of subjects who experienced =1 major adverse event (MAE) through 1 year post-treatment was less in the TAG subjects than in the Control subjects. The primary safety endpoint is a composite outcome consisting of the occurrence within 1 year post-procedure of any of the following MAEs:

- bleeding (procedural and post-procedural)
- coagulopathy
- hematoma
- atelectasis/pneumonia
- pulmonary embolism
- respiratory failure
- angina
- arrythmia
- CHF
- MI
- renal failure
- renal insufficiency
- wound dehiscence
- leg edema
- lymphocele/lymph fistula
- wound infection
- ileus
- bowel ischemia
- bowel obstruction
- amputation
- AV fistula
- embolism
- pseudoaneurysm
- restenosis
- thrombosis
- vascular trauma
- CVA
- mental status change
- femoral neuropathy
- nerve injury
- paraplegia/paraparesis
- spinal neurological deficit
- TIA
- anatomic false aneurysm
- aortoenteric fistula
- erectile dysfunction
- prothesis dilatation/rupture
- post-implant syndrome
- prosthetic infection
- prosthetic thrombosis
- reoperation
- death

Results: The proportion of subjects who experienced =1 MAE through 1 year post-treatment was significantly lower ($p < 0.001$) in the TAG (42%) vs. Control (77%) group. Ten (7.1%) TAG subjects had no 12-month follow-up visit. Assuming that all 10 TAG subjects experienced a MAE through 1 year post-treatment, the estimated 1-year MAE incidence in the TAG group increased from the 42% to 49%. However, the significance level for the comparison with the Control group remained < 0.001.

Confirmatory Study (TAG 03-03): The primary safety endpoint for the confirmatory study was the proportion of subjects who experienced =1 major adverse event (MAE) through 30 days post-treatment. Comparisons were made between subjects treated with the GORE TAG Thoracic Endoprosthesis (TAG) and open surgical repair (Control).

The safety null hypothesis was that the proportion of subjects who experienced =1 major adverse event (MAE) through 30 days post-treatment was equal in the Control subjects and the TAG subjects. The alternate hypothesis was that the proportion of subjects who experienced =1 major adverse event (MAE) through 30 days post-treatment was less in the TAG subjects than in the Control subjects. The primary safety endpoint is a composite outcome consisting of the occurrence within 30 days post-procedure of any of the MAEs as defined in TAG 99-01 and listed above.

Results: The proportion of subjects that experienced =1 MAE through 30 days post-treatment was significantly less ($p < 0.001$) in 03-03 TAG subjects (12%) compared to 99-01 Control subjects (70%).

Panel Question 1: Please comment on whether the results of the clinical studies with the above mentioned safety endpoints provide reasonable assurance of safety for the current device design in the intended population.

Effectiveness

Pivotal Study (TAG 99-01): The efficacy null hypothesis was that the proportion of subjects treated with the TAG device free from a major device-related event through the 12-month follow-up visit would be ≤ 0.8. The alternate hypothesis was that the proportion of subjects treated with the TAG device free from a major device-related event through the 12-month follow-up visit would be >0.8. This endpoint was a composite outcome consisting of subjects who were free from the following major device-related events: aneurysm enlargement, endoleaks, aneurysm rupture, branch vessel occlusion, deployment failure, extrusion/erosion, lumen obstruction, prothesis material failure, prosthesis migration, and prosthesis realignment.

When formalizing the efficacy hypotheses, the efficacy of open surgical repair was assumed to be 100%. A point estimate of 80% was judged to be a reasonable efficacy outcome for the endovascular treatment. The Agency and the sponsor agreed to an analysis plan where the device would need to show superior safety as the efficacy was expected to be less than that for surgical repair.

Results: The freedom from a major device-related event for the TAG device was 87 to 94 percent. Eight (6%) subjects experienced =1 major device-related event through the 12-month follow-up visit. The efficacy null hypothesis was that the proportion of subjects free from a major device-related event through the 12-month follow-up visit would be < 0.8. The resulting efficacy estimate was 0.94 with a lower bound 95% confidence interval of 0.90, and the null hypothesis was rejected ($p < 0.0001$) in favor of the alternate hypothesis that the probability was =0.8. These calculations assume that the 10 TAG subjects without a 12-month follow-up visit had no major device-related events. If one assumes that all 10 subjects without a 12-month follow-up visit had a major device-related event in this period, the estimate of the probability of not having a major device-related event was 0.87, and the null hypothesis was still rejected ($p = 0.02$, 1-sided).

Confirmatory Study (TAG 03-03): The primary efficacy endpoint was the proportion of subjects treated with the GORE TAG Thoracic Endoprosthesis who were free from a

major device-related event through the 30 day follow-up visit. Device-related events in the TAG group were presented descriptively.

Results: There were no major device-related events (no endoleaks, access failures, occlusion of branch vessel, prothesis migration, or aneurysm enlargement) through the 30-day follow-up visit in 03-03 TAG subjects compared to 6 (4%) subjects in the 99-01 TAG cohort. There were 6 (12%) subjects with minor endoleaks in the 03-03 TAG subjects, compared to 19 (14%) reported for the 99-01 TAG subjects. One subject with a minor proximal endoleak (noted 1-month procedure) and a distal endoleak (noted 92 days-post-procedure) underwent placement of 2 additional Gore TAG Endoprostheses 141 days post-procedure.

Panel Question 2: Please comment on whether the results of the clinical studies, with the above mentioned endpoints provides reasonable assurance of effectiveness for the current device design in the intended population.

Patient Comparability

In the pivotal study there was a statistically higher prevalence of symptomatic aneurysms in the open surgical repair control group as compared to the GORE TAG Thoracic Endoprosthesis (38% control, 21% TAG).

Panel Question 3: Please comment on whether the difference in the prevalence of symptomatic aneurysms is clinically significant and whether this affects your comments from questions 1 and 2.

Labeling

One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize clinical benefit and minimize adverse events. If you recommend approval of the device, please address the following questions regarding product labeling.

Panel Question 4: The proposed INDICATION FOR USE for this device is as follows: *Endovascular repair of aneurysm of the descending thoracic aorta*. Please comment on whether the indication for use adequately defines the patient population studied and for which the device will be marketed. Please address the need to include the required anatomical parameters for this device in the indications for use statement. (Note: As a point of reference, the indications for use of AAA approved endovascular grafts are attached as Appendix 1 to this document.)

Panel Question 5: Based on the clinical investigation experience, please comment on whether there are any additional warnings, precautions, or contraindications that you think should be included, either specific to this device or from a generic standpoint for endovascular grafts intended to treat thoracic aneurysms.

Panel Question 6: Please provide any additional comments you have on the labeling.

Training

Panel Question 7: Please comment on the adequacy of the proposed physician training plan, as described in the panel package (Appendix E).

Post-Market Study

Panel Question 8: Please comment on the adequacy of the proposed post-approval study plan, as described in the panel package (Appendix F).

Appendix 1

Indications for Use for Currently Approved Endovascular Grafts for Treatment of Abdominal Aortic Aneurysms

Cook, Inc.

The Zenith AAA Endovascular Graft with the H&L-B One-Shot? Introduction System and ancillary components is indicated for the endovascular treatment of patients with abdominal aortic, aortoiliac or iliac aneurysms having morphology suitable for endovascular repair, including:

- Adequate iliac/femoral access (?7.5 mm)
- Non-aneurysmal infrarenal neck length of at least 15 mm
- Neck diameter measured outer wall to outer wall of no greater than 28 mm and no less than 18 mm
- Iliac artery distal fixation site greater than 10 mm in length and no greater than 20 mm in diameter (measured outer wall to outer wall)
- One of the following:
  - An abdominal aortic aneurysm with a diameter ?4 cm
  - Aortic or aorto-iliac aneurysm with a history of growth ?0.5 cm per year

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The EXCLUDER Bifurcated Endoprosthesis is intended to exclude the aneurysm from the blood circulation in patients diagnosed with infrarenal abdominal aortic aneurysms (AAA) disease and who have appropriate anatomy as described below:

- adequate iliac/femoral access;
- infrarenal aortic neck treatment diameter range of 19-26 mm and a minimum aortic neck length of 15 mm;
- proximal aortic neck angulation <60°; and
- iliac artery treatment diameter range of 8-13.5 mm and iliac distal vessel seal zone length of at least 10 mm.

Guidant

The ANCURE Tube System is indicated for the endovascular treatment of infrarenal abdominal aortic aneurysms (AAA) in patients having:

- adequate iliac/femoral access;
- infrarenal non-aneurysmal neck length of at least 15 mm and a diameter of no greater than 26 mm;
- distal segment neck length of 12 mm and diameter of no greater than 26 mm; and
- morphology suitable for endovascular repair.

The ANCURE Bifurcated System is indicated for the endovascular treatment of infrarenal abdominal aortic or aorto-iliac aneurysms in patients having:

- adequate iliac/femoral access;
- infrarenal non-aneurysmal neck length of at least 15 mm and a diameter of no greater than 26 mm;
- distal segment lengths of at least 20 mm and diameters no greater than 13.4 mm; and
- morphology suitable for endovascular repair.

The ANCURE Aortoiliac System is indicated for the endovascular treatment of infrarenal abdominal aortic or aorto-iliac aneurysms in patients whose anatomy does not allow the use of a tube or bifurcated device and having:

- adequate iliac/femoral access;
- infrarenal non-aneurysmal neck length of at least 15 mm and a diameter of no greater than 26 mm;
- one distal segment length of at least 20 mm and diameters no greater than 13.4 mm; and
- morphology suitable for endovascular repair.

Medtronic

The AneuRx Stent Graft System is indicated for the endovascular treatment of infrarenal abdominal aortic or aorto-iliac aneurysms having:

- adequate iliac/femoral access;
- infrarenal, non-aneurysmal, neck length of greater than 1 cm at the proximal and distal ends of the aneurysm and an inner vessel diameter 10-20% smaller than the labeled device diameter;
- morphology suitable for endovascular repair; and
- one of the following:
  - aneurysm diameter >5 cm;
  - aneurysm diameter of 4-5 cm and which has also increased in size by 0.5 cm in the last 6 months; or
  - aneurysm which is twice the diameter of the normal infrarenal aorta.